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(54) Title: XANTHINES AND THEIR THERAPEUTIC USE

(57) Abstract

1,3-Disubstituted-zanthines have therapeutic utility via TNF or phosphodiesterase inhibition.

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XANTHINES AND THEIR THERAPEUTIC USE

Field of the invention

The present invention relates to novel xanthine compounds and pharmaceutically acceptable salts thereof, processes for their production and their formulation and use as pharmaceuticals.

Description of the prior art

Xanthine compounds such as theophylline (The Merck Index, 11th edition, 9212), pentoxifylline (The Merck Index, 11th edition 7092). and propentofylline (The Merck Index, 11th edition, 7822) have been widely used clinically for the treatment of respiratory tract disease or brain dysfunction. The chief clinical disadvantages of xanthine compounds are severe adverse reactions frequently induced by the administration of these compounds. Examples of the adverse reactions are, for example, cardio-excitatory activity such as, for example, cardiopalmus or tachycardia; central activity such as, for example, convulsion or headache; and gastrointestinal activity such as for example, nausea or emesis. Therefore, xanthine compounds without these adverse reactions would provide significant clinical benefit.

Related xanthine derivatives have been disclosed as pesticidal and pestistatic agents (United States Patent No. 4883801). In addition, related xanthine derivatives have been disclosed as intermediates but no pharmacological activity is disclosed for these compounds (European Patent Application No. 0 369 744, International Patent Application WO 92/05176, European Patent Application No. 0 389 282 and International Patent application WO 94/00452).

Phosphodiesterases regulate cyclic AMP concentrations. Phosphodiesterase IV has been demonstrated to be a principal regulator of cyclic AMP in respiratory smooth muscle and inflammatory cells. [See Torphy and Creslinski, *Molecular Pharmacology* 37, 206, (1990); Dent *et al British Journal of Pharmacology,* 90 163p (1990)]. Inhibitors of phosphodiesterase IV have been implicated as being bronchodilators and asthma-prophylactic agents and as agents for inhibiting eosinophil accumulation and the function of eosinophils [see for example Giembycz and Dent, *Clinical and Experimental Allergy* 22 337 (1992)] and for treating other diseases and conditions characterised by, or having an etiology including, morbid eosinophil accumulation. Inhibitors of phosphodiesterase IV are also implicated in treating inflammatory diseases, proliferative skin disease and conditions associated with cerebral metabolic inhibition.

Excessive or unregulated production of Tumour Necrosis Factor (TNF) has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis, in addition to a number of autoimmune diseases, such as multiple sclerosis, autoimmune diabetes and systemic lupus erythematosis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Viruses such as HIV-1 or HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication.

Cytokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by inhibition of cytokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as Kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg *et al*, The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli *et al*, Proc. Natl. Acad. Sci., 87:782-784, (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

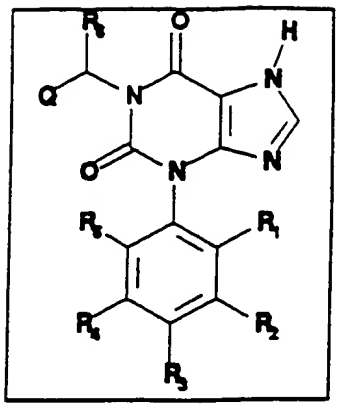
TNF has also been implicated in various roles with other viral infections, such as the cytomegalovirus (CMV), influenza virus, adenovirus, and the herpes virus for similar reasons as those noted above.

TNF is also associated with yeast and fungal infections. Specifically *Candida albicans* has been shown to induce TNF production *in vitro* in human monocytes and natural killer cells [See Riipi *et al.*, Infection and Immunity, 58(9):2750-54, (1990); and Jafari *et al.*, Journal of Infectious Diseases, 164:389-95, (1991). See also Wasan *et al.*, Antimicrobial Agents and Chemotherapy, 35, (10):2046-48, (1991); and Luke *et al.*, Journal of Infectious Diseases, 162:211-214, (1990)].

The ability to control the adverse effects of TNF is furthered by the use of the compounds which inhibit TNF in mammals who are in need of such use. There remains a need for compounds which are useful in treating TNF-mediated disease states which are exacerbated or caused by the excessive and/or unregulated production of TNF.

Summary of the invention

It has been found that novel compounds have ability to treat disease states, for example disease states associated with proteins that mediate cellular activity, for example by inhibiting tumour necrosis factor and/or by inhibiting phosphodiesterase IV. According to the invention, the novel compounds are of formula (i):

(i) 

in which Q represents aryl, heteroaryl, cycloalkyl or heterocyclo optionally substituted with one or more substituents chosen from amongst C_{1-6} alkyl (optionally substituted with one or more halogens), C_{1-6} alkyl-S(O)n- , $-CO_2H$ (or C_{1-6} alkyl esters thereof or C_{1-6} alkyl amides thereof), halogen, C_{1-6} alkoxy, CN, NO_2 or NR_7R_8 ;

R_1-R_5 , which may be the same or different, each represent C_{1-6} alkyl (optionally substituted with one or more halogens), C_{1-6} alkyl-S(O)n- , $-CO_2H$ (or C_{1-6} alkyl esters thereof or C_{1-6} alkyl amides thereof), halogen, C_{1-6} alkoxy, CN, NO_2, NR_7R_8 or H (provided R_1-R_6 are not all H simultaneously);

R_6 represents H, C_{1-6} alkyl, $-CO_2H$ (or C_{1-6} alkyl esters thereof or C_{1-6} alkyl amides thereof), -CN, C_{1-6} alkyl optionally substituted by $-CO_2H$ (or C_{1-6} alkyl esters thereof or C_{1-6} alkyl amides thereof), C_{1-6} alkoxy or -CN;

R_7 and R_8 , which may be the same or different, and each represent H, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl or C_{1-6} alkylsulphonyl, or R_7, R_8 and the nitrogen to which they are attached form a 5 or 6 membered heterocyclic ring (such as morpholine or piperidine); and

n represents 0-2;

and pharmaceutically acceptabl salts.

Description of the Invention

Preferred compounds of the invention include those in which, independently or in any combination:

Q is aryl or heteroaryl (either may be optionally substituted with halogen, C_{1-6} alkyl, CF_3, NR_7R_8, C_{1-6} alkyl-S(O)n- , C_{1-6} alkoxy, $-CO_2H$ (or C_{1-6} alkyl esters thereof or C_{1-6} alkyl amides thereof));

R_1-R_5, which may be the same or different, are independently CF_3, C_{1-6} alkyl, C_{1-6} alkyl-S(O)n-, $-CO_2H$ (or C_{1-6} alkyl esters thereof or C_{1-6} alkyl amides thereof), halogen, C_{1-6} alkoxy, NO_2, NR_7R_8 or H (provided R_1-R_5 are not all H simultaneously);

R_6 is H;

R_7 and R_8, which may be the same or different, are H, C_{1-6} alkyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulphonyl or C_{1-6} alkylcarbonyl; or R_7, R_8 and the nitrogen to which they are attached form a 5 or 6 membered heterocyclic ring (such as morpholine or piperidine); and

n is 0,1 or 2.

Suitable pharmaceutically acceptable salts are pharmaceutically acceptable base salts and pharmaceutically acceptable acid addition salts. Certain of the compounds of formula (i) which contain an acidic group form base salts. Suitable pharmaceutically acceptable base salts include metal salts, such as alkali metal salts for example sodium

salts, or organic amine salts such as that provided with ethylenediamine.

Certain of the compounds of formula (i) which contain an amino group form acid addition salts. Suitable acid addition salts include pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulphate, α-ketoglutarate, α-glycerophosphate and glucose-1-phosphate. The pharmaceutically acceptable salts of the compounds of formula (i) are prepared using conventional procedures.

It will be appreciated by those skilled in the art that xanthines of formula (i) can exist in more than one tautomeric form. This invention extends to all tautomeric forms.

It will be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted carbon and/or sulphur atoms. The presence of one or more of these asymmetric centers in a compound of formula (i) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers, and diastereoisomers and mixtures including racemic mixtures thereof.

When used herein the term alkyl whether used alone or when used as part of another group includes straight and branched chain alkyl groups containing up to 6 atoms. Cycloalkyl includes a non-aromatic cyclic or multicyclic ring system of about 3 to about 10 carbon atoms. Alkoxy means an alkyl-O- group in which the alkyl group is as previously described. Alkyl amide includes both monoalkyl

and dialkyl amides, in which the alkyl groups (previously defined) may be the same or different. Alkylcarbonyl means an alkyl-CO- group in which the alkyl group is as previously described. Aryl indicates a monocyclic or multicyclic carbocyclic radical containing about 6 to 10 carbon atoms. Heteroaryl means about a 5 to about a 10 membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the atoms in the ring system is an element other than carbon, chosen from amongst nitrogen, oxygen or sulphur. Heterocyclo means about a 5 to about a 10 membered saturated or partially saturated monocyclic or multicyclic hydrocarbon ring system in which one or more of the atoms in the ring system is an element other than carbon, chosen from amongst nitrogen, oxygen or sulphur. Arylcarbonyl means an aryl-CO- group. Heteroarylcarbonyl means a heteroaryl-CO- group. Heterocyclocarbonyl means a heterocyclo-CO- group. Arylsulphonyl means an aryl-SO_2- group. Heteroarylsulphonyl means a heteroaryl-SO_2- group. Heterocyclosulphonyl means a heterocyclo-SO_2- group. Alkylsulphonyl means an alkyl-SO_2- group. Halogen means fluorine, chlorine, bromine or iodine.

"TNF mediated disease or disease states" means any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance, is a major component, and whose production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF-β (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-α and TNF-β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

This invention relates to a method for mediating or inhibiting the enzymatic activity or catalytic activity of PDE IV in a mammal in need thereof and for inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (i) or a pharmaceutically acceptable salt thereof.

PDE IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases, including: asthma, chronic bronchitis, atopic dermatitis, atopic eczema, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, psoriasis, Bechet's disease, erythematosis, anaphylactoid purpura nephritis, joint inflammation, arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis and osteoarthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alzheimer's disease), memory impairment associated with Parkinson's disease, depression and multi-infarct dementia. PDE IV inhibitors are also useful in conditions ameliorated by neuroprotectant activity, such as cardiac arrest, stroke and intermittent claudication. Additionally, PDE IV inhibitors could have utility as gastroprotectants. A special embodiment of the therapeutic methods of the present invention is the treatment of asthma.

The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased

replication, directly or indirectly, by the TNF inhibitors of Formula (i). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes zoster* and *Herpes simplex*.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (i) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be also be used in association with the veterinary treatment of animals, other than humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anaemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of this invention are also useful in treating parasite, yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis.

The compounds of formula (i) are preferably in pharmaceutically acceptable form. By pharmaceutically acceptable form is meant, *inter alia*, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically acceptable level of purity will generally

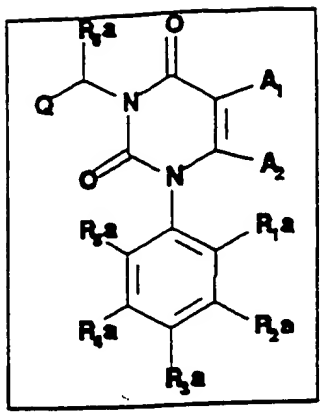
be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%.

The invention further provides a process for the preparation of a compound of formula (i), in which R_1-R_6 are as defined above. It will be appreciated that functional groups such as amino, hydroxyl or carboxyl groups present in the various compounds described below, and which it is desired to retain, may need to be in protected forms before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction. Suitable protecting groups for such functionality will be apparent to those skilled in the art. For specific details, see Protective Groups in Organic Synthesis, Wiley Interscience, TW Greene.

Thus the process required for preparing compounds of formula (i) in which R_6 is $-CO_2H$ comprises of deprotecting (for example by hydrolysis) a compound of formula (i) in which R_6 is $-CO_2R$ wherein R represents a suitable protecting group (eg, methyl).

It will be appreciated that where a particular stereoisomer of formula (i) is required, this may be obtained by conventional resolution techniques such as high performance liquid chromatography or the synthetic processes herein described may by performed using the appropriate homochiral starting material.

A process for the preparation of a compound of formula (i) comprises a dehydrating cyclisation of a compound of formula (ii):-



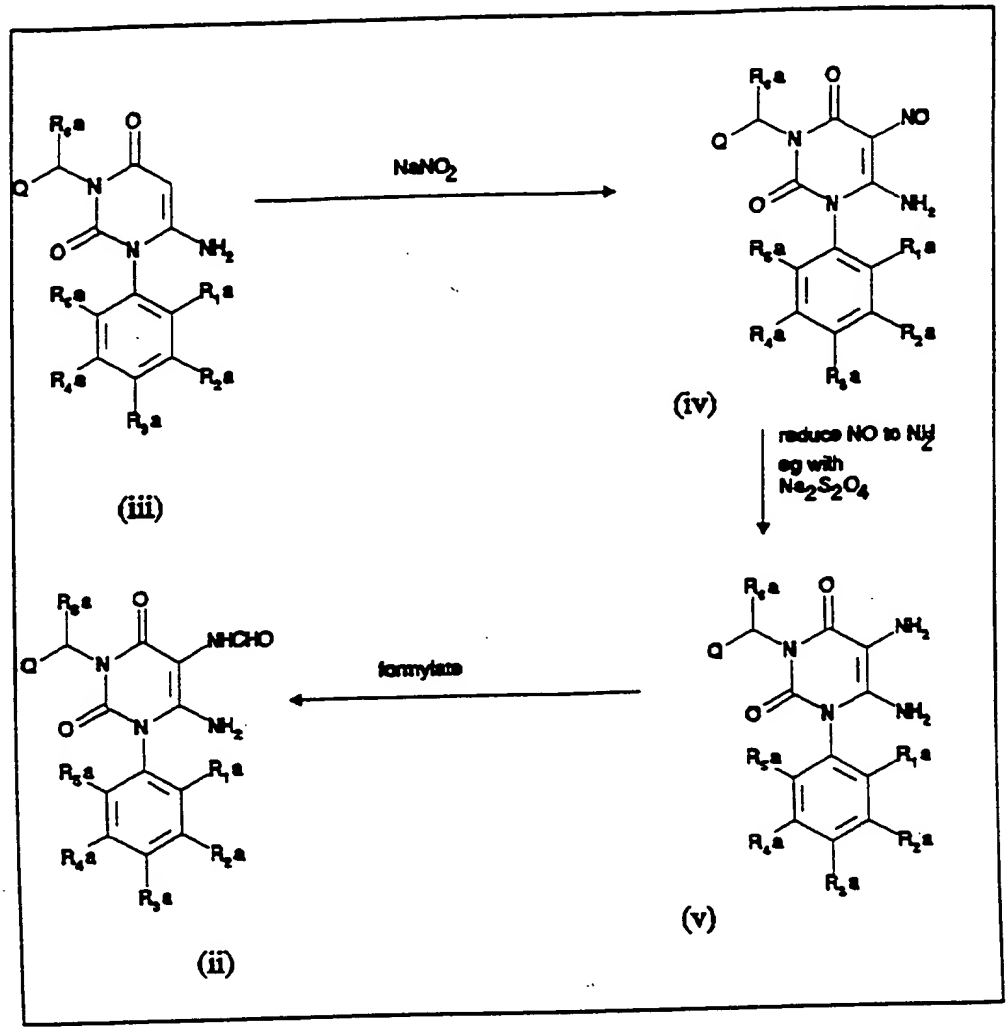
(ii)

wherein R_{1a} represents R_1, as defined in relation to formula (i), or a group convertable to R_1, and R_{2a}-R_{6a} similarly represent R_2-R_6 or groups convertable to R_2-R_6, respectively; A_1 represents -NO or -NHCHO and A_2 represents $-NHCH_3$ or $-NH_2$, providing that when A_1 is -NO then A_2 is $NHCH_3$ and when A_1 is NHCHO then A_2 is NH_2; and thereafter, if required, converting any group R_{1a} to R_1 and/or R_{2a} to R_2 and/or R_{3a} to R_3 and/or R_{4a} to R_4 and/or R_{5a} to R_5 and/or R_{6a} to R_6. The dehydrating cyclisation of a compound of formula (ii) may be carried out under any suitable conditions known to those skilled in the art. Favourably the conditions chosen are those wherein the water formed is removed from the reaction mixture, thus the reaction is generally carried out at an elevated temperature in the range 100°C to 200°C, such as in the range 180°C to 190°C.

In one aspect of the process, especially when A_1 is -NO and A_2 is $-NHCH_3$, the reaction is carried out in a solvent immiscible with water, such as toluene, at the reflux temperature of the solvent, the water being removed using a water separator.

A compound of formula (ii) wherein A_1 represents -NHCHO and A_2 represents $-NH_2$ may be suitably prepared from a 6-

aminouracil of formula (iii) according to the following reaction scheme:-



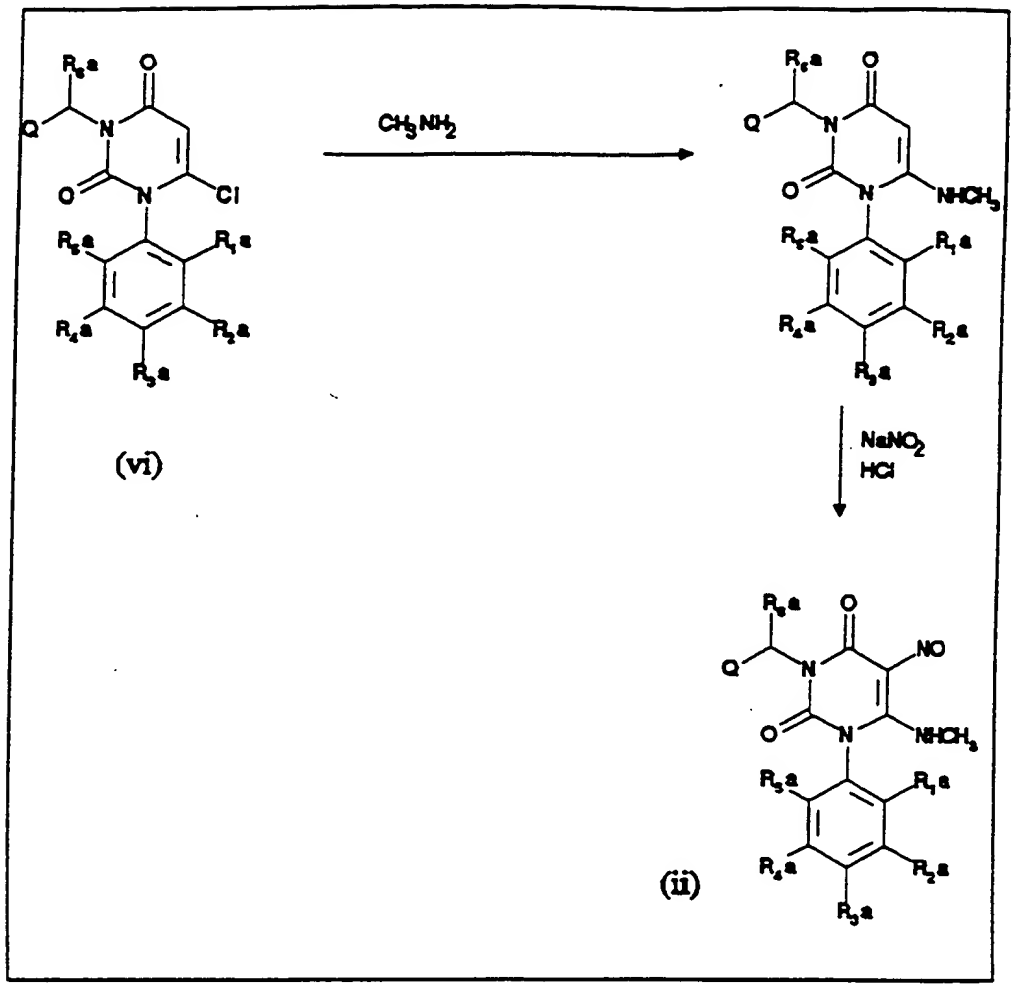
wherein R_{1a}-R_{6a} are as defined in relation to formula (ii).

Suitably, the reaction conditions used in the above reaction scheme are appropriate conventional conditions known to those skilled in the art. In a preferred aspect of the process, the conversion of the 6-aminouracil (iii), via (iv) and (v), to the corresponding compound of formula (ii) and the cyclisation of the compound of formula (ii) to

the compound of formula (i) are all carried out *in situ*, suitably by using an analogous procedure to that of H. Bredereck and A. Edenhofer, *Chem. Berichte* 88 1306-1312 (1955).

The 6-aminouracils of formula (iii) may themselves be prepared by the method of V. Papesch and E. F. Schroder, *J. Org. Chem.* 16 1879-90 (1951), or Yozo Ohtsuka, *Bull. Chem. Soc. Jap.* 46(2) 506-9 (1973) or modifications of these methods.

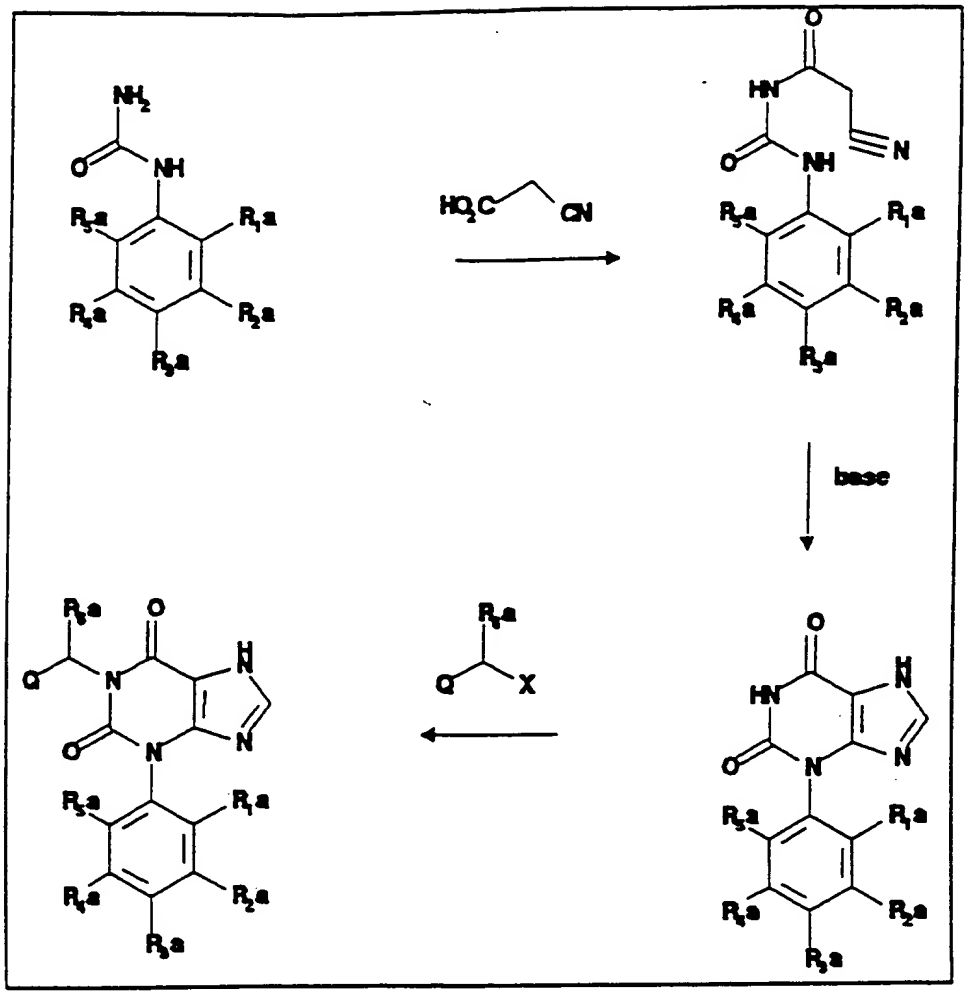
A compound of formula (ii) wherein A_1 represents -NO and A_2 represents $-NHCH_3$ may conveniently be prepared from a 6-chlorouracil of formula (vi) according to the following reaction scheme:-



wherein R_{1a}-R_{6a} are as defined in relation to formula (ii).

Suitably, the reaction conditions used in the above scheme are the appropriate conventional conditions, for example those used in the method of H. Goldner, G. Dietz and E. Carstens, *Liebigs Annalen der Chemie* 691 142-158 (1965). The 6-chlorouracil of formula (vi) may also be prepared according to the procedure of Dietz *et al*.

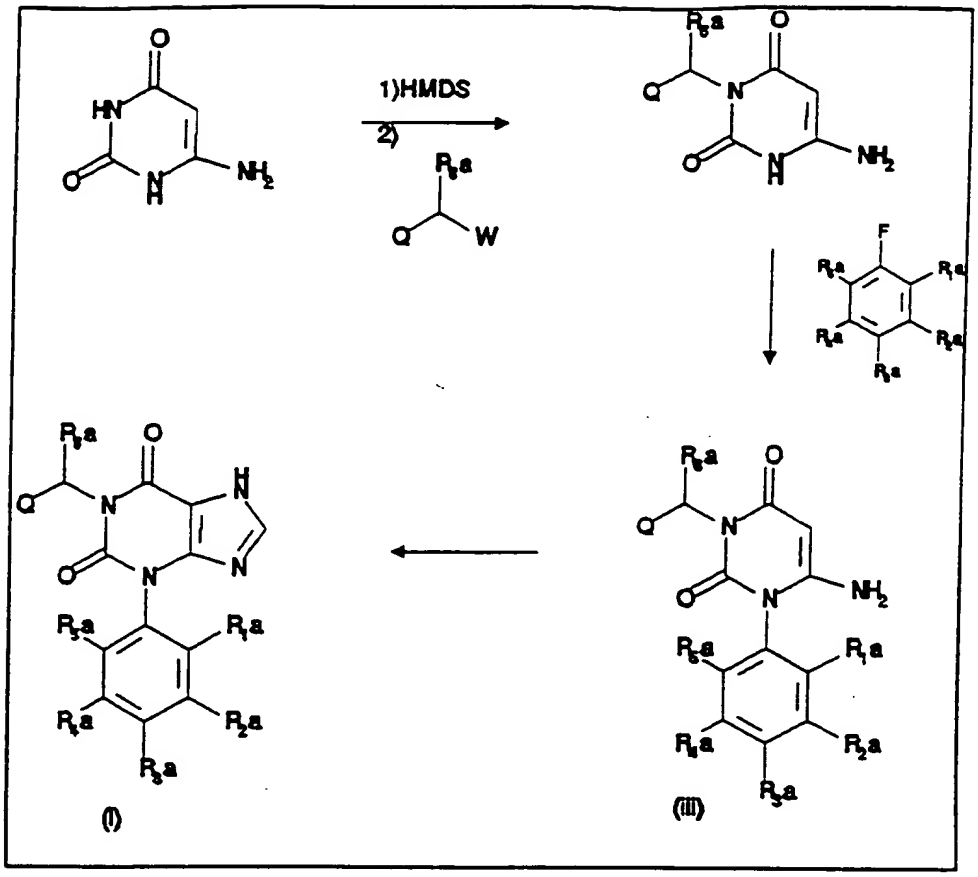
Alternatively, compounds of formula (i) may be prepared according to the following reaction scheme:-



(i)

wherein R_{1a}-R_{6a} are as defined in relation to formula (ii) and X is an appropriate leaving group such as bromo. Suitably the reaction conditions used in the above reaction scheme are standard conditions known to those skilled in the art.

Another method for the preparation of some compounds of formula (i) (based on a method described by C. E. Muller, D. Shi, M. Manning and J. W. Daly in *J. Med. Chem.* 36 3341 (1993)) is shown in the following reaction scheme:-



wherein R_{1a}-R_{6a} are as defined in relation to formula (ii) and W represents a leaving group such as bromo. It will be appreciated by those skilled in the art that this method will not be applicable if any of R_{1a}-R_{5a} represents fluoro.

Compounds of formula (i) may also be prepared by interconversion of other compounds of formula (i). Thus, for example, a compound of formula (i) in which R_1 is NH_2 may be prepared by reduction of a compound of formula (i) in which R_1 is $-NO_2$.

A compound of formula (i) or where appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered *per se* or, preferably, as a pharmaceutical

composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (i) or where appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier.

The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc, the compounds of the invention are effective in the treatment of humans.

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers for example microcrystalline cellulose, lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methylcellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-

hydroxybenzoate or sorbic acid; and if desired conventi nal flavouring or colouring agents.

Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebuliser, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 microns, such as from 0.1 to 50 microns, preferably less than 10 microns, for example from 1 to 10 microns, 1 to 5 microns or from 2 to 5 microns. Where appropriate, small amounts of other anti-asthmatics and bronchodilators for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the

composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

Compounds of formula (i), or if appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be administered as a topical formulation in combination with conventional topical excipients.

Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings, gels, gel sticks, spray and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

Suitable cream, lotion, gel, stick, ointment, spray or aerosol formulations that may be used for compounds of formula (i) or if appropriate a pharmaceutically acceptable salt thereof, are conventional formulations well known in the art, for example, as described in standard text books such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

Suitably, the compound of formula (i), or if appropriate a pharmaceutically acceptable salt thereof, will comprise from about 0.5 to 20% by weight of the formulation, favourably from about 1 to 10%, for example 2 to 5%.

The dose of the compound used in the treatment of the invention will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and the relative efficacy of the compound. However, as a general guide suitable unit doses may be 0.1 to 1000mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10mg, for example 0.5, 1, 2, 3, 4 or 5mg; and such unit doses may be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70kg adult is in the range of about 0.1 to 1000mg, that is in the range of about 0.001 to 20 mg/kg/day, such as 0.007 to 3, 0.007 to 1.4, 0.007 to 0.14 or 0.01 to 0.5mg/kg/day, for example 0.01, .0.02, 0.04, 0.05, 0.06, 0.08, 0.1 or 0.2 mg/kg/day, and such therapy may extend for a number of weeks or months.

When used herein the term "pharmaceutically acceptable" encompasses materials suitable for both human and veterinary use.

The following illustrates the invention.

Intermediate 1 **2-(METHYLTHIO)PHENYLISOCYANATE**

2-Methylmercaptoaniline (69.5g) was dissolved in ethanol and treated at 0°C portionwise with concentrated hydrochloric acid (75ml). The resulting solid was obtained by filtration, washed with isopropanol and dried *in vacuo*.

This solid was finely ground, suspended in dry dioxane (500ml) and treated with trichloromethylchloroformate (27ml) and the mixture refluxed for 18 hours under nitrogen. The solvent was carefully removed *in vacuo* and the product obtained by distillation. Yield=24.14g

bp 116-118°C (15mm Hg)

Intermediate 2 **2-(METHYLTHIO)BENZYLAMINE**

A solution of 2-(methylthio)benzonitrile (29.8g) in dry ether (150ml) was added dropwise to a stirred suspension of lithium aluminium hydride (11.6g) in dry ether (360ml) under nitrogen. A thick gum formed which was dissolved by the addition of dry THF (100ml). The mixture was stirred at room temperature for 2 hours. Water (12ml) was then carefully added followed by a 15% aqueous solution of sodium hydroxide (36ml) and more water (12ml). The mixture was filtered, the filtrate washed with water, dried and evaporated *in vacuo*. The residue was distilled *in vacuo* to give a colourless oil. Yield=20.9g.

bp 139-141°C (15mm Hg)

Intermediate 3 **1-BENZYL-3-[3-(METHYLTHIO)PHENYL]UREA**

Method A

3-(Methylthio)aniline (22.24g,) was dissolved in dry toluene (300ml) and to this was added benzyl isocyanate (19.95g) with stirring. Very soon a thick deposit was formed and stirring was no longer possible. The resulting mixture was allowed to stand overnight at room temperature and hexane (250ml) then added. The product was filtered off and washed with 1:1 toluene/hexane. Yield=38.89g.

mp 127-129°C

Intermediate 4 **1-BENZYL-3-(3-CHLOROPHENYL)UREA**

Method B

3-Chlorophenylisocyanate (30.7g) was dissolved in dry toluene (400ml) and benzylamine (23.54g) added in one portion with stirring. The mixture was stirred for 30min

at room temperature and the pr duct then filtered off and washed with toluene then hexane. Yield=47.53g.

mp 172-174°C

Intermediate 5 **1-BENZYL-3-(4-CHLOROPHENYL)UREA**

Method C

Benzylamine (26.75g) was dissolved in dry toluene (800ml) and to this was added 4-chlorophenyl isocyanate (38.38g) with stirring. After the exotherm had subsided the mixture was heated to boiling and then allowed to stand overnight at room temperature. The product was filtered off and washed with toluene. Yield=64g.

mp 202-204°C

Intermediate 6 **1-BENZYL-3-[3(METHOXYCARBONYL)PHENYL]UREA**

Method A, mp 148-151°C

Intermediate 7 **1-BENZYL-3-(4-METHOXYPHENYL)UREA**

Method B, mp 164-167°

Intermediate 8 **1-BENZYL-3-(4-FLUOROPHENYL)UREA**

Method B, mp 181-183°C

Intermediate 9 **1-BENZYL-3-(3-FLUOROPHENYL)UREA**

Method B, mp 158-160°C

Intermediate 10 **1-BENZYL-3-[4(METHYLTHIO)PHENYL]UREA**

Method A, mp 173-176°C

Intermediate 11 1-BENZYL-3-(3-METHOXYPHENYL)UREA

Method A, mp 159-161°C

Intermediate 12 1-BENZYL-3-(3-BROMOPHENYL)UREA

Method A, mp 173-175°C

Intermediate 13 1-BENZYL-3-(3-NITROPHENYL)UREA

Method A, mp 193-195°C

Intermediate 14 1-(THEN-2-YL)-3-(2-METHYLPHENYL)UREA

Method B, mp 188-190°C

Intermediate 15 1-FURFURYL-3-(2-METHYLPHENYL)UREA

Method B, mp 117-119°C

Intermediate 16 1-(2-FLUOROBENZYL)-3-(4-CHLOROPHENYL)UREA

Method B, mp 195-198°C

Intermediate 17 1-[2-(TRIFLUOROMETHYL)BENZYL]-3-(2-METHYL-PHENYL)UREA

Method A, mp 190-192°C

Intermediate 16 1-BENZYL-3-(2-METHYLPHENYL)UREA

Method A, mp 189-190°C

Intermediate 18 1-(2-FLUOROBENZYL)-3-(2-FLUOROPHENYL)UREA

Method B, mp 160-163°C

Intermediate 19 1-(2-FLUOROBENZYL)-3-[2-(METHYLTHIO)-PHENYL]UREA

Method B, mp 135-137°C

Intermediate 20 1-(2-FLUOROBENZYL)-3-[2-(TRIFLUOROMETHYL)-PHENYL]UREA

Method A, mp 178-181°C

Intermediate 21 1-(2-FLUOROBENZYL)-3-(2-NITROPHENYL)UREA

Method A, mp 169-172°C

Intermediate 22 1-(2-METHYLPHENYL)-3-[2-(METHYLTHIO)-BENZYL]UREA

Method A, mp 214-216°C

Intermediate 23 1-BENZYL-3-(3-CHLOROPHENYL)-1-(CYANOACETYL)UREA

A mixture of 1-benzyl-3-(3-chlorophenyl)urea (44.78g) and cyanoacetic acid (16.11g) was ground together and then acetic anhydride (48ml) added. The resulting mixture was heated and stirred at 75-80°C for 16h. It was then allowed to cool, diluted with ether and the product filtered off and washed with ether. This was then recrystallised from toluene with a hot filtration. Yield=20.15g.

mp 122-123°C

The following intermediates were prepared using the above procedure.

Intermediate 24 **1-BENZYL-1-(CYANOACETYL)-3-[3-(METHOXYCARBONYL)PHENYL]UREA**

The crude material was dissolved in hot toluene and treated with charcoal. The charcoal was removed by filtration and the product recrystallised from toluene.

mp 134-137°C

Intermediate 25 **1-BENZYL-3-(4-CHLOROPHENYL)-1-(CYANOACETYL)UREA**

mp 100-104°C

Intermediate 26 **1-BENZYL-1-(CYANOACETYL)-3-[3-(METHYLTHIO)PHENYL]UREA**

mp 113-116°C

Intermediate 27 **1-BENZYL-1-(CYANOACETYL)-3-(4-METHOXYPHENYL)UREA**

The crude material was dissolved in hot toluene and treated with charcoal. The charcoal was removed by filtration and the product recrystallised from toluene/hexane.

mp 114-117°C

Intermediate 28 **1-BENZYL-1-(CYANOACETYL)-3-(3-FLUOROPHENYL)UREA**

mp 97-99°C

Intermediate 29 **1-BENZYL-1-(CYANOACETYL)-3-[4-(METHYLTHIO)-PHENYL]UREA**

mp 128-130°C

Intermediate 30 **1-BENZYL-1-(CYANOACETYL)-3-(3-METHOXY-PHENYL)UREA**

The crude material was dissolved in hot toluene and treated with charcoal. The charcoal was removed by filtration and the product recrystallised from toluene.

mp 127-130°C

Intermediate 31 **1-BENZYL-3-(3-BROMOPHENYL)-1-(CYANO-ACETYL)UREA**

The crude material was dissolved in hot toluene and treated with charcoal. The charcoal was removed by filtration and the product recrystallised from toluene/hexane.

mp 108-121°C

Intermediate 32 **1-(THEN-2-YL)-3-(2-METHYLPHENYL)-1-(CYANO-ACETYL)UREA**

mp 127-130°C

Intermediate 33 **1-FURFURYL-3-(2-METHYLPHENYL)-1-(CYANO-ACETYL)UREA**

mp 117-119°C

Intermediate 34 **1-(2-FLUOROBENZYL)-3-(4-CHLOROPHENYL)-1-(CYANOACETYL)UREA**

This product was washed with ethanol.

mp 125-134°C

Intermediate 35 **6-AMINO-3-BENZYL-1-[3-(METHYLTHIO)-PHENYL]URACIL**

1-Benzyl-1-(cyanoacetyl)-3-[3-(methylthio)phenyl]urea (14.9g) was suspended in ethanol (150ml) and to this was added a solution of sodium hydroxide (2.34g) in water (30ml). This was stirred for 1h then allowed to stand overnight at room temperature. The mixture was filtered to remove a dark impurity and the filtrate carbon treated. This solution was then evaporated to remove ethanol then diluted with water. It was extracted with ethyl acetate (150ml) and the extracts washed with water (2x75ml) then dried and evaporated to give a foam. This was taken up in a 1:1 mixture of ethyl acetate and toluene (100ml). After standing for 1h the product had precipitated. It was filtered off and washed with 1:1 toluene/hexane (50ml) then dried to constant weight. Yield=9.06g.

mp 168-170°C

Intermediate 36 **6-AMINO-3-BENZYL-1-[3-(METHOXYCARBONYL)-PHENYL]URACIL**

1-Benzyl-1-(cyanoacetyl)-3-[3-(methoxycarbonyl)phenyl]urea (3.51g) was dissolved in dichloromethane (50ml) and triethylamine (1.52g) added. The mixture was stirred for one hour at room temperature and the product filtered off and washed with dichloromethane. Yield=3.16g.

mp 208-210°C

The following intermediates were prepared using the above procedure.

Intermediate 37 6-AMINO-3-BENZYL-1-(4-METHOXYPHENYL)URACIL

mp 219-221°C

Intermediate 38 6-AMINO-3-BENZYL-1-(4-CHLOROPHENYL)URACIL

mp 246-248°C

Intermediate 39 6-AMINO-3-(THEN-2-YL)-1-(2-METHYLPHENYL)URACIL

mp 253-256°C

Intermediate 40 6-AMINO-3-FURFURYL-1-(2-METHYLPHENYL)URACIL

mp 241-244°C

Intermediate 41 6-AMINO-3-(2-FLUOROBENZYL)-1-(4-CHLOROPHENYL) URACIL

The crude material was dissolved in hot ethanol and treated with charcoal. The charcoal was removed by filtration and the product recrystallised from ethanol.

mp 192-212°C

Intermediate 42 6-AMINO-3-BENZYL-1-(3-FLUOROPHENYL)URACIL

mp 228-230°C

Intermediate 43 **6-AMINO-3-BENZYL-1-[4-(METHOXYTHIO)PHENYL] URACIL**

mp 132-133°C

Intermediate 44 **6-AMINO-3-BENZYL-1-(3-METHOXYPHENYL)URACIL**

The product was recrystallised from ethanol.

mp 211-214°C

Intermediate 45 **6-AMINO-3-BENZYL-1-(4-FLUOROPHENYL)URACIL**

1-Benzyl-1-(cyanoacetyl)-3-(4-fluorophenyl) urea was prepared from the appropriate benzyl urea using the procedure described in the preparation of intermediate 22. The oil produced was used in the above procedure (Intermediate 36) to yield the title compound. Recrystallised from ethyl acetate.

mp 214-217°C

The following intermediates were prepared using the above procedure.

Intermediate 46 **6-AMINO-1-(2-METHYLPHENYL)-3-[2-(TRIFLUORO-METHYL)BENZYLURACIL**

The resulting residue was subjected to column chromatography on silica eluting with ethyl acetate to furnish the title compound.

mp 209-218°C

Intermediate 47 **6-AMINO-3-BENZYL-1-(2-METHYLPHENYL)URACIL**

The crude material was dissolved in hot ethanol and treated with charcoal. The charcoal was removed by filtration and the product recrystallised from ethanol.

mp 194-197°C

Intermediate 48 **6-AMINO-3-(2-FLUOROBENZYL)-1-(2-FLUOROPHENYL)URACIL**

mp 207-208°C

Intermediate 49 **6-AMINO-3-(2-FLUOROBENZYL)-1-[2-(METHYLTHIO)-PHENYL]URACIL**

mp 214-216°C

Intermediate 50 **6-AMINO-3-(2-FLUOROBENZYL)-1-[2-(TRIFLUORO-METHYLPHENYL]URACIL**

mp 259-263°C

Intermediate 51 **6-AMINO-3-(2-FLUOROBENZYL)-1-(2-NITROPHENYL)URACIL**

mp 250-255°C

Intermediate 52 **6-AMINO-3-BENZYL-1-(3-NITROPHENYL)URACIL**

1-Benzyl-3-(3-nitrophenyl)urea (32.53g) and cyanoacetic acid (11.24g) were ground together and acetic anhydride (34ml) was added. The mixture was stirred and heated at 75-80°C for 30h. It was then evaporated, taken up in

boiling toluene and treated with charcoal. The charcoal was removed by filtration. The resulting solution was allowed to c ol and left to stand overnight at room temperature. The resulting solid was filtered off and washed with ether. This solid was dissolved in dichloromethane (100ml) and triethylamine (3.57g) added.

The filtrate was also treated with triethylamine (8.55g). These two solutions were allowed to stand overnight and the precipitated solids were filtered off, washed with dichloromethane and combined to give the title compound (11.32g).

mp 256-260°C

Intermediate 53 **6-AMINO-1-(2-METHYLPHENYL)-3-[2-(METHYLTHIO)-BENZYL]URACIL**

1-(2-Methylphenyl)-3-[2-(methylthio)benzyl]urea (23.47g) and cyanoacetic acid (7.66g) were ground together and acetic anhydride (23ml) was added. The mixture was stirred and heated at 75-80°C for 30h. Toluene (20ml) was then added and heating continued for a further 16 hours. The reaction was cooled and filtered. The filtrate was heated to boiling and treated with charcoal. The solid was removed by filtration and the filtrate evaporated *in vacuo*. The resulting oil was dissolved in dichloromethane (300ml) and triethylamine (8.15g) added. The mixture was stirred for 5 hours at room temperature and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica gel eluting with ethyl acetate and the product was recrystallised from ethyl acetate. Yield=2.60g.

mp 218-221°C

Example 1 **1-BENZYL-3-(3-METHOXYPHENYL)XANTHINE**

A mixture of 6-amino-3-benzyl-1-(3-methoxyphenyl)uracil (5.52g), formic acid (3.2ml) and sodium nitrite (1.45g) in formamide (130ml) was gradually heated up to 100°C with stirring. Sodium dithionite (4.83g) was then added in portions over a period of 10 min, the temperature being held at 100°C. The temperature was then raised to 190°C and the mixture stirred at this temperature for 30 min. It was allowed to cool then extracted into chloroform. The chloroform solution was extracted into 2M sodium hydroxide solution and this washed with ether. The aqueous layer was acidified with concentrated hydrochloric acid to give a solid which was filtered off and washed with water. Recrystallisation from ethanol provided the title compound (1.55g).

TLC R_f 0.33 (5%methanol/dichloromethane)

mp 205-208°C

This general procedure was used for all the following xanthines.

Example 2 **1-BENZYL-3-(3-CHLOROPHENYL)XANTHINE**

6-Amino-3-benzyl-1-(3- chlorophenyl) uracil was prepared using the procedure described for intermediate 36. The foam produced was used in the procedure of example 1 to yield the title product.

TLC R_f 0.33 (5%methanol/dichloromethane)

mp 245-248°C

Example 3 **1-BENZYL-3-(3-FLUOROPHENYL)XANTHINE**

Recrystallised from ethanol.

TLC R_f 0.51 (5%methanol/dichloromethane)

mp 203-204°C

Example 4 1-BENZYL-3-[3-(METHYLTHIO)PHENYL]XANTHINE

Recrystallised from ethanol.

TLC R_f 0.44 (5%methanol/dichloromethane)

mp 191-193°C

Example 5 1-BENZYL-3-(4-METHOXYPHENYL)XANTHINE

Recrystallised from ethanol.

TLC R_f 0.30 (5%methanol/dichloromethane)

mp 242-244°

Example 6 1-BENZYL-3-(4-FLUOROPHENYL)XANTHINE

Recrystallised from ethanol.

TLC R_f 0.30 (5%methanol/dichloromethane)

mp 252-255°C

Example 7 1-BENZYL-3-[4-(METHYLTHIO)PHENYL]XANTHINE

Recrystallised from ethanol/DMF.

TLC R_f 0.44 (5%methanol/dichloromethane)

mp 260-264°C

Example 8 1-BENZYL-3-(3-BROMOPHENYL)XANTHINE

6-Amino-1-(3-bromophenyl)-3-benzyluracil was prepared using the procedure described in the preparation of Intermediate 36. The foam produced was used in the procedure of example 1 to yield the title compound.

Recrystallised from ethanol.

TLC R_f 0.49 (5%methanol/dichloromethane)

mp 253-256°C

Example 9 **1-BENZYL-3-(3-NITROPHENYL)XANTHINE**

Recrystallised from acetonitrile.

TLC R_f 0.42 (5%methanol/dichloromethane)

mp 227-229°C

Example 10 **1-(THEN-2-YL)-3-(2-METHYLPHENYL)XANTHINE**

Recrystallised from ethanol.

TLC R_f 0.35 (ethyl acetate)

mp 258-262°C

Example 11 **1-(2-FLUOROBENZYL)-3-(4-CHLOROPHENYL)-XANTHINE**

Recrystallised from acetonitrile/DMF.

TLC R_f 0.41 (ethyl acetate)

mp 329-331°C

Exampl 12 **1-BENZYL-3-(2-METHYLPHENYL)XANTHINE**

Recrystallised from ethanol.

TLC R_f 0.33 (ethyl acetate)

mp 266-269°C

Example 13 **1-(2-FLUOROBENZYL)-3-(2-FLUOROPHENYL)-XANTHINE**

Recrystallised from ethanol.

TLC R_f 0.35 (ethyl acetate)

mp 253-256°C

Example 14 **1-BENZYL-3-(4-CHLOROPHENYL)XANTHINE**

Recrystallised from acetonitrile/DMF.

TLC R_f 0.41 (ethyl acetate)

mp 310-313°C

Example 15 **1-[2-(TRIFLUOROMETHYL)BENZYL]-3-(2-METHYLPHENYL)XANTHINE**

Recrystallised from ethanol.

TLC R_f 0.36 (ethyl acetate)

mp 282-285°C

Example 16 **1-(2-FLUOROBENZYL)-3-[2-(METHYLTHIO)PHENYL]XANTHINE**

Recrystallised from acetonitrile.

TLC R_f 0.31 (ethyl acetate)

mp 274-279°C

Example 17 1-(2-FLUOROBENZYL)-3-[2-(TRIFLUOROMETHYL) PHENYL]XANTHINE

Recrystallised from ethanol.

TLC R_f 0.31 (ethyl acetate)

mp 273-277°C

Example 18 1-(2-FLUOROBENZYL)-3-(2-NITRO PHENYL)XANTHINE

TLC R_f 0.31 (ethyl acetate)

mp 210-255°C

Example 19 1-(2-FLUOROBENZYL)-3-[2-(TRIFLUOROMETHYL) PHENYL]XANTHINE

Recrystallised from ethanol.

TLC R_f 0.34 (ethyl acetate)

mp 220-233°C

The following two compounds were prepared using the general procedure with a modified work up as follows:-

Example 20 1-BENZYL-3-[3-(METHOXYCARBONYL)-PHENYL]XANTHINE

On cooling, the reaction mixture was extracted with chloroform. The extracts were washed with water, dried then evaporated. The resulting residue was subjected to column chromatography on silica eluting with ethyl acetate to yield the titled compound.

TLC R_f 0.33 (5%methanol/dichloromethane)

mp 230-232°C

Example 21 **1-FURFURYL-3-(2-METHYLPHENYL)XANTHINE**

Recrystallised from ethanol.

TLC R_f 0.35 (ethyl acetate)

mp 257-260°C

Example 22 **3-(3-AMINOPHENYL)-1-BENZYLXANTHINE**

1-Benzyl-3-(3-nitrophenyl)xanthine (1g) was added to a solution of stannous chloride dihydrate (2.51g) in concentrated hydrochloric acid (5ml) and the mixture heated to 60-70°C with stirring and held at this temperature for 20 min. The reaction mixture was allowed to cool and 40% sodium hydroxide (11ml) added. The mixture was cooled and the solid filtered off and washed with water (10ml). It was taken up in 2M sodium hydroxide (10ml), treated with charcoal, filtered, and the filtrate acidified with glacial acetic acid. The product was filtered off and washed with water. Yield 0.44g.

TLC R_f 0.24 (5%methanol/dichloromethane)

mp 320-323°C

Example 23 **3-(2-AMINOPHENYL)-1-(2-FLUOROBENZYL)XANTHINE**

The title compound was prepared using the above procedure.

Recrystallised from acetonitrile.

TLC R_f 0.23 (ethyl acetate)

mp 316-319°C (d)

Example 24 **3-(3-ACETAMIDOPHENYL)-1-BENZYLXANTHINE**

3-(3-Aminophenyl)-1-benzyl xanthine (0.68g) was suspended in glacial acetic acid (30ml). To this was added acetic anhydride (0.25g) and the mixture was stirred at reflux for 1h. Water (30ml) was then added and the product filtered off then washed with water (30ml). Yield 0.55g.

TLC R_f 0.19 (5%methanol/dichloromethane)

mp >300°C

Example 25 **1-(2-FLUOROBENZYL)-3-[2-(METHYLSULPHONYL)-PHENYL]XANTHINE**

A solution of 1-(2-fluorobenzyl)-3-[2-(methylthio)phenyl]xanthine (2.8g) in chloroform (600ml) and methanol (15ml) was stirred and maintained below 10°C during the addition of 3-chloroperbenzoic acid (3.45g of 80% material). The mixture was stirred for 4 hours at room temperature and then more 3-chloroperbenzoic acid (0.7g of 80% material) added. The reaction was stirred overnight and then treated with sodium bicarbonate (2.1g) in water (100ml). The mixture was stirred for one hour, filtered and the filtrate evaporated *in vacuo*. The residue was slurried with water, filtered and the solid washed with water. Recrystallised from ethanol/DMF. Yield=1.44g

TLC R_f 0.19 (ethyl acetate)

mp 264-270°C

Example 26 **1-(2-FLUOROBENZYL)-3-[2-(METHYLSULPHINYL)-PHENYL]XANTHINE**

A solution of 1-(2-fluorobenzyl)-3-[2-(methylthio)phenyl]xanthine (1.15g) in chloroform (200ml) and methanol (5ml) was stirred and maintained at 0-2°C during the addition of 3-chloroperbenzoic acid (0.65g of 80% material). The mixture was stirred for 4 hours at 0°C and then more 3-chloroperbenzoic acid (0.06g of 80% material) added. The reaction was stirred for one hour at 0°C and then overnight at room temperature. The mixture was treated with calcium hydroxide (0.3g). The mixture was stirred for one hour, filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in dichloromethane, washed with saturated aqueous sodium bicarbonate and then extracted into 1M aqueous sodium hydroxide solution (2x100ml). The extracts were washed with dichloromethane and the aqueous layer acidified with concentrated hydrochloric acid to give an oil. The oil was extracted with dichloromethane, dried, filtered and the filtrate evaporated to give a solid. The solid was triturated with ether and obtained by filtration. Yield=0.53g

TLC R_f 0.05 (ethyl acetate)

mp 230-233°C(dec.)

Example 27 **1-(2-FLUOROBENZYL)-3-(2-METHYLPHENYL)-XANTHINE**

ortho-Tolylisocyanate (4.95ml) was added to a solution of 2-fluorobenzylamine (4.56ml) in toluene (50ml) under an atmosphere of nitrogen at 5ºC to produce rapid formation of a white solid. Heptane was added, the solid broken up and filtered off to afford 1-(2-fluorobenzyl)-3-(2-

methylphenyl)urea (9.5g) as a white solid. The urea (8g) and cyanoacetic acid (2.9g) were ground together and heated in acetic anhydride (15ml) to 80ºC. After cooling the reaction mixture to room temperature, diethyl ether was added and washed with water. The separated ether phase was dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a crude solid residue (8.9g). This residue was redissolved in dichloromethane (120ml), triethylamine (5.7ml) added and the mixture stirred at room temperature for 3 days. Filtration of the precipitate yielded the desired uracil as a white solid (2.6g).

The title compound was prepared from this uracil following the general procedure with a modified work up. After the reaction mixture was allowed to cool to room temperature it was extracted into dichloromethane. Attempted extraction into aqueous sodium bicarbonate solution failed to provide any product. However the product precipitated out of the dichloromethane solution and was collected by filtration to afford a white solid (273mg).

mp 276-277ºC

TLC R_f0.11 (50% ethyl acetate in hexane)

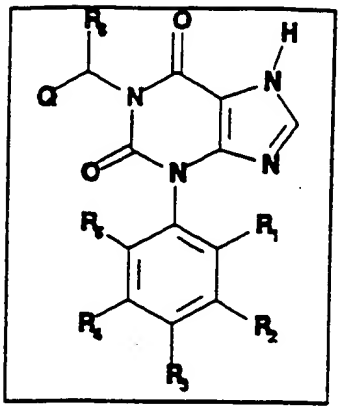
Assay methods

The methods used to confirm the phosphodiesterase IV inhibitory activity of compounds of formula (i) are standard assay procedures as disclosed by Schilling *et al* *Anal. Biochem.* 216 154 (1994), Thompson and Strada *Adv. Cycl. Nucl. Res.* 8 119 (1979) and Gristwood and Owen *Br. J. Pharmacol.* 87 91P (1986).

Compounds of formula (i) have exhibited activity at levels consistent with those believed to be useful in treating phosphodiesterase IV related disease states in those assays.

CLAIMS

1. Compounds of the general formula (i):



(i)

in which Q represents aryl, heteroaryl, cycloalkyl or heterocyclo optionally substituted with one or more substituents chosen from C_{1-6} alkyl (optionally substituted with one or more halogens), C_{1-6} alkyl-S(O)n- (where n is 0, 1 or 2), $-CO_2H$ (or C_{1-6} alkyl esters thereof or C_{1-6} alkyl amides thereof), halogen, C_{1-6} alkoxy, CN, NO_2 and NR_7R_8;

R_1-R_5 , which may be the same or different, each represent C_{1-6} alkyl (optionally substituted with one or more halogens), C_{1-6} alkyl-S(O)n- (where n is 0, 1 or 2), $-CO_2H$ (or C_{1-6} alkyl esters thereof or C_{1-6} alkyl amides thereof), halogen, C_{1-6} alkoxy, CN, NO_2, NR_7R_8 or H (provided R_1-R_6 are not all H simultaneously);

R_6 represents H, C_{1-6} alkyl, $-CO_2H$ (or C_{1-6} alkyl esters thereof or C_{1-6} alkyl amides thereof), -CN, C_{1-6} alkyl optionally substituted by $-CO_2H$ (or C_{1-6} alkyl esters thereof or C_{1-6} alkyl amides thereof), C_{1-6} alkoxy or -CN; and

R_7 and R_8, which may be the same or different, each represent H, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl or C_{1-6} alkylsulphonyl, or R_7, R_8 and the nitrogen to which they are attached form a 5 or 6 membered heterocyclic ring (such as morpholine or piperidine);

and pharmaceutically-acceptable salts thereof.

2. A compound of claim 1, wherei R_7 and R_8 are independently selected from H, alkyl, alkylcarbonyl, alkoxycarbonyl, arylsulphonyl, arylcarbonyl and alkylsulphonyl, or NR_7R_8 is a ring.

3. A compound of claim 1 or claim 2, wherein Q is aryl or heteroaryl, either of which is optionally substituted by halogen, alkyl, CF_3, NR_7R_8, alkyl$S(O)_{0-2}$, alkoxy or COOH (or esters or amides thereof).

4. A compound of any preceding claim, wherein R_1-R_5 are independently selected from CF_3, alkyl, alkyl$S(O)_{0-2}$, COOH (or esters or amides thereof), halogen, alkoxy, NO_2, NR_7R_8 and H.

5. A compound of claim 2 wherein Q is phenyl; R_1-R_5 are independently selected from alkyl$S(O)_{0-2}$, COOH (or esters or amides thereof), halogen, alkoxy, NO_2, NR_7R_8 and H; and R_7 and R_8 are independently selected from H, alkyl, alkylcarbonyl, alkoxycarbonyl, arylsulphonyl, arylcarbonyl and alkylsulphonyl.

6. A compound of any preceding claim, wherein R_6 is H.

7. A compound of claim 1, selected from

1-benzyl-3-(3-methoxyphenyl)xanthine,

1-benzyl-3-(3-chlorophenyl)xanthine,

1-benzyl-3-(3-fluorophenyl)xanthine,

1-benzyl-3-[3-(methylthio)phenyl]xanthine,

1-benzyl-3-(4-methoxyphenyl)xanthine,

1-benzyl-3-(4-fluorophenyl)xanthine,

1-benzyl-3-[4-(methylthio)phenyl]xanthine,

1-benzyl-3-(3-bromophenyl)xanthine,

1-benzyl-3-(3-nitrophenyl)xanthine and

1-benzyl-3-[3-(methoxycarbonyl)-phenyl]xanthine.

8. A compound of claim 1, selected from 1-benzyl-3-(2-methylphenyl)xanthine and 1-(2-fluorobenzyl)-3-(2-methylphenyl)xanthine.

9. A compound of claim 1, selected from

1-(then-2-yl)-3-(2-methylphenyl)xanthine,

1-(2-fluorobenzyl)-3-(4-chlorophenyl)xanthine,

1-(2-fluorobenzyl)-3-(2-fluorophenyl)xanthine,

1-benzyl-3-(4-chlorophenyl)xanthine,

1-[2-(trifluoromethyl)benzyl]-3-(2-methylphenyl)xanthine,

1-(2-fluorobenzyl)-3-[2-(methylthio)phenyl]xanthine,

1-(2-fluorobenzyl)-3-[2-(trifluoromethyl)phenyl]xanthine,

1-(2-fluorobenzyl)-3-(2-nitrophenyl)xanthine,

1-(2-fluorobenzyl)-3-[2-(trifluoromethyl)phenyl]xanthine,

1-furfuryl-3-(2-methylphenyl)xanthine,

3-(3-aminophenyl)-1-benzylxanthine,

3-(2-aminophenyl)-1-(2-fluorobenzyl)xanthine,

3-(3-acetamidophenyl)-1-benzylxanthine,

1-(2-fluorobenzyl)-3-[2-(methylsulphonyl)phenyl]xanthine and

1-(2-fluorobenzyl)-3-[2-(methylsulphinyl)-phenyl]xanthine.

10. A compound of any preceding claim, in the form of an enantiomer or diestereoisomer, or any mixture of either.

11. A pharmaceutical composition containing a compound according to any of claims 1 to 10 as active ingredient, in combination with suitable excipients.

12. A method for treating a disease state capable of being modulated by inhibiting production of phosphodiesterase IV, comprising administering to a patient suffering from said disease an effective amount of a compound according to any of claims 1 to 10.

13. The method of claim 12, wherein the disease state is a pathological condition associated with a function of phosphodiesterase IV, eosinophil accumulation or a function of the eosinophil.

14. The method of claim 13, wherein the pathological condition is selected from asthma, chronic bronchitis,

at pic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal c njunctivitis, inflammati n of the eye, allergic responses in the eye, eosinophilic granul ma, psoriasis, rheumatoid arthritis, gouty arthritis and other arthritic conditions, ulcerative colitis, Crohn's disease, adult respiratory distress syndrome, diabetes insipidus, keratosis, atopic dermatitis, atopic eczema, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, depression, cardiac arrest, stroke and intermittent claudication.

15. The method of claim 14, wherein the pathological condition is asthma.

16. A method for treating a disease state capable of being modulated by inhibiting TNF, comprising administering to a patient suffering from said disease an effective amount of a compound according to any of claims 1 to 10.

17. The method of claim 16, wherein the disease state is an inflammatory disease or autoimmune disease.

18. The method of claim 17, wherein the disease state is selected from joint inflammation, arthritis, rheumatoid arthritis, rheumatoid spondylitis and osteoarthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, asthma, bone resorption diseases, reperfusion injury, graft vs host reaction, allograft rejection, fever and myalgias due to infection, such as influenza, malaria, myalgias, HIV, AIDS, ARC, cachexia, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes mellitus, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic

glomerulonephritis, inflammatory bowel disease and leukaemia.

19. The method of claim 18, wherein the disease state is joint inflammation.

20. The method of claim 12 or claim 16, wherein the disease state is tardive dyskinesia.

21. The method of claim 16, wherein the disease state is a yeast or fungal infection.

22. A method for gastroprotection, comprising administering to a patient in need thereof an effective amount of a compound according to any of claims 1 to 10.

INTERNATIONAL SEARCH REPORT

Inter... al Application No
PCT/GB 96/01202

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D473/06 C07D473/04 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 05175 (BEECHAM GROUP PLC) 2 April 1992 see page 0	1-11
A	WO,A,92 11260 (BEECHAM GROUP PLC) 9 July 1992 see page 0	1-11
A	WO,A,86 01724 (THE GENERAL HOSPITAL CORPORATION) 27 March 1986 cited in the application see page 30 - page 31; claim 1	1
A	& US,A,4 883 801 (THE GENERAL HOSPITAL CORPORATION) cited in the application	

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 1996	05.07.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Luyten, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 96/01202

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 369 744 (BEECHAM WUELFING GMBH & CO KG) 23 May 1990 cited in the application see page 0	1-11
A	WO,A,92 05176 (BEECHAM GROUP PLC) 2 April 1992 cited in the application	1-11
A	EP,A,0 389 282 (BEECHAM-WUELFING GMBH &CO KG) 26 September 1990 cited in the application see page 1 - page 2	1-11
A	WO,A,94 000 452 (MALESCI INSTITUTO FARMACOBIOLOGICO S.P.A.) 6 April 1994 cited in the application see page 0	1-11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/GB96/01202

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-22 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/GB 96/01202

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		CA-A-	2092430	27-03-92
		EP-A-	0550570	14-07-93
		JP-T-	6501251	10-02-94
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INTERNATIONAL SEARCH REPORT

information on patent family members

Intern al Application No
PCT/GB 96/01202

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